Developmental and Reproductive Toxicant Identification Committee
c/o Ms. Michelle Ramirez
Office of Environmental Health Hazard Assessment
Proposition 65 Implementation Office
P.O. Box 4010, MS-12B
1001 I Street
Sacramento, California 95814

October 24, 2017

Re: Consideration of chlorpyrifos for possible Prop 65 listing based on developmental toxicity

Dear Chairperson Gold and Developmental and Reproductive Toxicant Identification Committee Members,

The following comments are submitted on behalf of the Natural Resources Defense Council (NRDC), California Rural Legal Assistance Fund (CRLAF), Center for Environmental Health (CEH) and Pesticide Action Network (PAN), which do not have any financial interest in the topic of these comments. We submit these comments to draw the committee's attention to 37 additional studies with findings relevant to the developmental neurotoxicity of chlorpyrifos. Taken altogether, the evidence in these studies and the hazard identification materials provided by Office of Environmental Health Hazard Assessment (OEHHA) meet the requirement under Prop65 for listing as a developmental toxicant.

The DARTIC hazard identification materials being provided to the committee include the US EPA 2014 and 2016 Revised Human Health Risk Assessments, as well as bibliographies of the papers cited therein. There is also a provided bibliography of additional studies that were not cited in these assessments; this bibliography includes studies in two different populations that demonstrated changes in infant development following prenatal exposure to chlorpyrifos.[1]

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[1] Kyle R Fluegge, Marcia Nishioka, and J R Wilkins, "Effects of Simultaneous Prenatal Exposures to Organophosphate and Synthetic Pyrethroid Insecticides on Infant Neurodevelopment at Three Months of Age.," *Journal of Environmental Toxiology and Public Health* 1 (May 2016): 60–73, doi:10.5281/zenodo.218417; Monica K Silver et al.,

We have performed a literature review and found 37 additional relevant articles regarding the question of whether chlorpyrifos has been shown through valid scientific testing to cause developmental or reproductive toxicity. These articles were found by searching pubmed and medline using one of five sets of search terms (chlorpyrifos AND [2017 OR neurodevelopment OR children OR infants], or organophosphates AND neurodevelopment). These articles are not listed in either of the bibliographies that are being officially submitted to the committee, and many of them were only published in the last year. In addition to the other literature provided to the DARTIC, this collection of papers adds further evidence of chlorpyrifos as a developmental and reproductive toxicant. Therefore, we would like to respectfully submit the attached annotated bibliography for the committee's review.

The attached annotated bibliography is organized into five sections. Headers indicate the section and within each section, the articles are alphabetical by first author.

I. **Chlorpyrifos specific studies**
   a. highly relevant review article (1 paper)
   b. epidemiologic studies (2 papers)
   c. animal studies (7 papers)
   d. bench studies (4 studies)

II. **Important organophosphate studies to consider**
   a. relevant review articles on organophosphates (8 papers)
   b. epidemiologic studies (15 papers)

From this list of papers, we would like to highlight the recent review article by Burke et al, which was published in August 2017, and provides an excellent synthesis of the current state of knowledge on the subject. Based on a review of mechanistic, animal, and human studies the authors conclude that chlorpyrifos has been shown to cause neurodevelopmental toxicity in bench and animal studies, with epidemiologic studies that show neurodevelopmental effects for the class of organophosphate pesticides (of which chlorpyrifos is one example).[2]

In considering the question of neurodevelopmental toxicity of chlorpyrifos we urge the DARTIC to consider the following:

- <u>US EPA's summary and determination in the 2014 and 2016 Risk Assessments of developmental neurotoxicity at levels below that which result in</u>

"Prenatal Naled and Chlorpyrifos Exposure Is Associated with Deficits in Infant Motor Function in a Cohort of Chinese Infants.," *Environment International* 106 (September 2017): 248–56, doi:10.1016/j.envint.2017.05.015.

[2] Richard D Burke et al., "Developmental Neurotoxicity of the Organophosphorus Insecticide Chlorpyrifos: From Clinical Findings to Preclinical Models and Potential Mechanisms.," *Journal of Neurochemistry* 142, no. 2 (August 2017): 162–77, doi:10.1111/jnc.14077.

acetylcholinesterase inhibition [3].

- Evidence from Epidemiological studies
  In addition to the Columbia Study cited by USEPA, there are 4 studies in human populations linking chlorpyrifos specific biomarkers to neurodevelopmental deficits. These include 2 studies from the bibliography provided by OEHHA[4] and 2 additional studies summarized here finding that adolescents who worked applying chlorpyrifos had neurobehavioral changes[5] and school aged children with higher chlorpyrifos exposure had lower cognitive performance.[6]

- Animal and mechanistic studies
  The bench studies show that chlorpyrifos exposure causes damage to neurons[7] and neural precursor cells,[8] with changes that occur through a variety of mechanisms including acetylcholinesterase inhibition as well as others[9]. Chlorpyrifos-induced damage seems to be worst in cells that are actively differentiating. Consistent with these findings, the recent animal studies show

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[3] USEPA, "Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review.," (Washington DC, 20460, November 3, 2016); USEPA, "Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review.," December 29, 2014, 1–531.
[4] Fluegge, Nishioka, and Wilkins, "Effects of Simultaneous Prenatal Exposures to Organophosphate and Synthetic Pyrethroid Insecticides on Infant Neurodevelopment at Three Months of Age.;" Silver et al., "Prenatal Naled and Chlorpyrifos Exposure Is Associated with Deficits in Infant Motor Function in a Cohort of Chinese Infants.."
[5] Ahmed A Ismail et al., "The Impact of Repeated Organophosphorus Pesticide Exposure on Biomarkers and Neurobehavioral Outcomes Among Adolescent Pesticide Applicators.," *Journal of Toxicology and Environmental Health, Part A* 80, no. 10 (2017): 542–55, doi:10.1080/15287394.2017.1362612.
[6] Berna van Wendel de Joode et al., "Pesticide Exposure and Neurodevelopment in Children Aged 6-9 Years From Talamanca, Costa Rica.," *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior* 85 (December 2016): 137–50, doi:10.1016/j.cortex.2016.09.003.
[7] Xian Wu et al., "From the Cover: AstrocytesAre Protective Against Chlorpyrifos Developmental Neurotoxicity in Human Pluripotent Stem Cell-Derived Astrocyte-Neuron Cocultures.," *Toxicological Sciences : an Official Journal of the Society of Toxicology* 157, no. 2 (June 1, 2017): 410–20, doi:10.1093/toxsci/kfx056.
[8] Jeong Eun Lee et al., "Nuclear NF-κB Contributes to Chlorpyrifos-Induced Apoptosis Through P53 Signaling in Human Neural Precursor Cells.," *Neurotoxicology* 42 (May 2014): 58–70, doi:10.1016/j.neuro.2014.04.001.
[9] Paula Moyano et al., "Toxicogenomic Profile of Apoptotic and Necrotic SN56 Basal Forebrain Cholinergic Neuronal Loss After Acute and Long-Term Chlorpyrifos Exposure.," *Neurotoxicology and Teratology* 59 (February 2017): 68–73, doi:10.1016/j.ntt.2016.10.002; Abayomi A Adigun et al., "Organophosphate Exposure During a Critical Developmental Stage Reprograms Adenylyl Cyclase Signaling in PC12 Cells.," *Brain Research* 1329 (May 6, 2010): 36–44, doi:10.1016/j.brainres.2010.03.025.

that chlorpyrifos exposure induced behavioral changes in guinea pigs[10], mice,[11] and multiple kinds of fish[12]. Chlorpyrifos exposure also affected fertility in male rats,[13] and was particularly harmful to Huntington's diseased neural cells.[14]

- <u>Evidence from Studies on the class of Organophosphates</u>
  The evidence from non-specific organophosphate exposure markers also provides important information for consideration of the impacts of chlorpyrifos on the developing brain. As outlined by the EPA in their 2015 review of the neurodevelopmental hazards of organophosphates (OPs),[15] a "literature review of *in vivo* laboratory animal studies and epidemiology studies for OPs other than chlorpyrifos [can] support the single chemical HHRAs [human health risk assessments]."

  Thus, complementing those studies regarding chlorpyrifos specifically, another fifteen articles demonstrate a relationship between organophosphate exposure

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[10] Burke et al., "Developmental Neurotoxicity of the Organophosphorus Insecticide Chlorpyrifos: From Clinical Findings to Preclinical Models and Potential Mechanisms.."
[11] Pia Basaure et al., "Two Cholinesterase Inhibitors Trigger Dissimilar Effects on Behavior and Body Weight in C57BL/6 Mice: the Case of Chlorpyrifos and Rivastigmine.," *Behavioural Brain Research* 318 (February 1, 2017): 1–11, doi:10.1016/j.bbr.2016.10.014.
[12] Melissa Faria et al., "Zebrafish Is a Predictive Model for Identifying Compounds That Protect Against Brain Toxicity in Severe Acute Organophosphorus Intoxication.," *Archives of Toxicology* 91, no. 4 (April 2017): 1891–1901, doi:10.1007/s00204-016-1851-3; Xuchun Qiu et al., "Short-Term and Persistent Impacts on Behaviors Related to Locomotion, Anxiety, and Startle Responses of Japanese Medaka (Oryzias Latipes) Induced by Acute, Sublethal Exposure to Chlorpyrifos.," *Aquatic Toxicology (Amsterdam, Netherlands)* 192 (September 14, 2017): 148–54, doi:10.1016/j.aquatox.2017.09.012; Paul J Van den Brink, Sylvan L Klein, and Andreu Rico, "Interaction Between Stress Induced by Competition, Predation, and an Insecticide on the Response of Aquatic Invertebrates.," *Environmental Toxicology and Chemistry* 36, no. 9 (September 2017): 2485–92, doi:10.1002/etc.3788; Jiayu Zhang et al., "The Single and Joint Toxicity Effects of Chlorpyrifos and Beta-Cypermethrin in Zebrafish (Danio Rerio) Early Life Stages.," *Journal of Hazardous Materials* 334 (July 15, 2017): 121–31, doi:10.1016/j.jhazmat.2017.03.055.
[13] Dinithi Champika Peiris and Thamali Dhanushka, "Low Doses of Chlorpyrifos Interfere with Spermatogenesis of Rats Through Reduction of Sex Hormones.," *Environmental Science and Pollution Research - International* 24, no. 26 (July 18, 2017): 20859–67, doi:10.1007/s11356-017-9617-x.
[14] Gifty A Dominah et al., "Acute Exposure to Chlorpyrifos Caused NADPH Oxidase Mediated Oxidative Stress and Neurotoxicity in a Striatal Cell Model of Huntington's Disease.," *Neurotoxicology* 60 (May 2017): 54–69, doi:10.1016/j.neuro.2017.03.004.
[15] USEPA, "Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides," September 15, 2015.

and neurodevelopmental outcomes including decreased intelligence in children[16], changes in infant brain development[17] and birth outcomes[18]. These effects seem to be worst in children whose mothers have low PON1 enzyme activity.[19]

Per the 1993 guidance to the DART committee,[20] a chemical can be listed as causing developmental harm if it "meets one of the following criteria:

- sufficient evidence of reproductive toxicity in humans, or
- limited evidence or suggestive evidence in humans, supported by sufficient experimental animal (mammal) data, or
- sufficient evidence in experimental animals (mammals), such that extrapolation

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[16] Chloé Cartier et al., "Organophosphate Insecticide Metabolites in Prenatal and Childhood Urine Samples and Intelligence Scores at 6 Years of Age: Results From the Mother-Child PELAGIE Cohort (France).," *Environmental Health Perspectives* 124, no. 5 (May 2016): 674–80, doi:10.1289/ehp.1409472; Eric Coker et al., "Association Between Pesticide Profiles Used on Agricultural Fields Near Maternal Residences During Pregnancy and IQ at Age 7 Years.," *International Journal of Environmental Research and Public Health* 14, no. 5 (May 9, 2017): 506, doi:10.3390/ijerph14050506; B González-Alzaga et al., "A Systematic Review of Neurodevelopmental Effects of Prenatal and Postnatal Organophosphate Pesticide Exposure.," *Toxicology Letters* 230, no. 2 (October 15, 2014): 104–21, doi:10.1016/j.toxlet.2013.11.019; Robert B Gunier et al., "Prenatal Residential Proximity to Agricultural Pesticide Use and IQ in 7-Year-Old Children.," *Environmental Health Perspectives* 125, no. 5 (May 25, 2017): 057002, doi:10.1289/EHP504; Ahmed A Ismail et al., "Comparison of Neurological Health Outcomes Between Two Adolescent Cohorts Exposed to Pesticides in Egypt.," *PLoS ONE* 12, no. 2 (2017): e0172696, doi:10.1371/journal.pone.0172696; Christopher Rowe et al., "Residential Proximity to Organophosphate and Carbamate Pesticide Use During Pregnancy, Poverty During Childhood, and Cognitive Functioning in 10-Year-Old Children.," *Environmental Research* 150 (October 2016): 128–37, doi:10.1016/j.envres.2016.05.048.

[17] Pornpimol Kongtip et al., "The Impact of Prenatal Organophosphate Pesticide Exposures on Thai Infant Neurodevelopment.," *International Journal of Environmental Research and Public Health* 14, no. 6 (May 27, 2017): 570, doi:10.3390/ijerph14060570.

[18] Warangkana Naksen et al., "Associations of Maternal Organophosphate Pesticide Exposure and PON1 Activity with Birth Outcomes in SAWASDEE Birth Cohort, Thailand.," *Environmental Research* 142 (October 2015): 288–96, doi:10.1016/j.envres.2015.06.035; Pei Wang et al., "Organophosphate Pesticide Exposure and Perinatal Outcomes in Shanghai, China.," *Environment International* 42 (July 2012): 100–104, doi:10.1016/j.envint.2011.04.015.

[19] Brenda Eskenazi et al., "Organophosphate Pesticide Exposure, PON1, and Neurodevelopment in School-Age Children From the CHAMACOS Study.," *Environmental Research* 134 (October 2014): 149–57, doi:10.1016/j.envres.2014.07.001.

[20] OEHHA, "Criteria for Recommending Chemicals for Listing as Known to the State to Cause Reproductive Toxicity," November 1, 1993.

to humans is appropriate."

The summarized science includes evidence of developmental toxicity in humans and substantial evidence in animal data, and therefore meets these criteria.

Thus, the evidence cited in the two EPA human health risk assessments, plus the additional scientific literature summarized here constitute valid scientific evidence demonstrating that chlorpyrifos causes developmental toxicity, with some evidence of reproductive toxicity as well. In addition to strong bench and animal evidence, there are four additional human epidemiologic studies that have been published since the EPA health hazard assessments were completed (two included in our bibliography, and two in the bibliography provided to your committee of studies that had not been cited). Chlorpyrifos therefore warrants Prop 65 listing and we appreciate your review of the evidence.

Sincerely,

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Part One: Chlorpyrifos Specific Studies

Part 1a. Chlorpyrifos Specific Studies: Highly Relevant Review Article

Burke RD, Todd SW, Lumsden E, et al. Developmental neurotoxicity of the organophosphorus insecticide chlorpyrifos: from clinical findings to preclinical models and potential mechanisms. *J Neurochem*. 2017;142 Suppl 2(S2):162-177. doi:10.1111/jnc.14077.

- Recent review article summarizing the developmental neurotoxicity from chlorpyrifos.
- Notes that chlorpyrifos crosses the placenta
- There is good evidence that in a longitudinal cohort, chlorpyrifos exposure was associated with reduced weight and length at birth, impaired cognition and memory at age 3, decreased IQ and working memory at age 7 and tremors at age 11.
- Children exposed to chlorpyrifos prenatally showed structural changes in their brains at age 7-9.
- Many studies have shown associations between organophosphate exposures and neurologic deficits in both adults and children.
- Mice and rats exposed to chlorpyrifos show changes in behavior, dependent on the timing of exposure. Some of the changes are different by sex (for example, cognitive deficits that are more pronounced in female rats and mice following prenatal exposure). These changes seem to be independent of acetylcholinesterase inhibition.
- Guinea pigs, which are considered by some to be a better model for human neurodevelopment, were exposed to chlorpyrifos prenatally and had learning deficits and decreases in frontal brain volume which correlate with those deficits. “The findings that guinea pigs subjected to prenatal subacute exposure to CPF presented spatial learning deficits that were sexually dimorphic and correlated with disruption of the structural integrity of different brain regions are in line with reports that: (i) correlations between prenatal CPF exposure and cognitive deficits in children are generally stronger among boys than girls (Marks et al. 2010; Horton et al. 2012; Rauh et al. 2012), and (ii) normal correlations between FSIQ and the surface area of different brain regions were either absent or reversed among children, particularly boys, who experienced prenatal exposures producing cord blood levels of CPF ≥ 4.39 ng/g (Rauh et al. 2012).” (from p171)
- Mechanistic studies have shown that chlorpyrifos has non-acetylcholinesterase effects, and learning and behavioral findings often do not correlate with the acetylcholinesterase inhibition, suggesting that chlorpyrifos has other effects and can cause effects at levels lower than previously thought.
- Other possible mechanisms that have been evaluated for neurotoxicity include oxidative stress, perturbations in Ca2+ homeostasis, increased inflammatory mediators, increased activity of protein kinases and changes in neutrophin signaling.
- “It is in this context that preclinical studies become extremely relevant. Various preclinical research groups throughout the world have consistently demonstrated that CPF is a developmental neurotoxicant.” (p.173)

Part 1b. Chlorpyrifos Specific Studies: Epidemiologic Studies

Ismail AA, Wang K, Olson JR, et al. The impact of repeated organophosphorus pesticide exposure on biomarkers and neurobehavioral outcomes among adolescent pesticide applicators. *Journal of Toxicology and Environmental Health, Part A*. 2017;80(10-12):542-555. doi:10.1080/15287394.2017.1362612.

- Study of Egyptian adolescent pesticide applicators (ages 12-21) which found an inverse association between chlorpyrifos urinary biomarker (TCPy) and deficits in neurobehavioral performance tasks.
- Eighty-four adolescents were followed through two pesticide application seasons.
- TCPy levels, a questionnaire and neurobehavioral battery were completed before and after each pesticide application season
- Current TCPy levels were significantly associated with multiple different neurobehavioral deficits.

van Wendel de Joode B, Mora AM, Lindh CH, et al. Pesticide exposure and neurodevelopment in children aged 6-9 years from Talamanca, Costa Rica. *Cortex*. 2016;85:137-150. doi:10.1016/j.cortex.2016.09.003.

- Cross sectional study of 140 children (ages 6-9) living near banana plantations in Costa Rica
- Inverse relationship between chlorpyrifos biomarker concentrations and multiple cognitive domains, some of which varied by sex
- Higher TCPy concentrations were associated with poorer working memory in boys, poorer visual motor coordination, increased parent reported inattention, increased oppositional disorders and decreased color discrimination.

Part 1c. Animal Studies

Basaure P, Peris-Sampedro F, Cabré M, Reverte I, Colomina MT. Two cholinesterase inhibitors trigger dissimilar effects on behavior and body weight in C57BL/6 mice: The case of chlorpyrifos and rivastigmine. *Behav Brain Res*. 2017;318:1-11. doi:10.1016/j.bbr.2016.10.014.

- Rat study looking at chlorpyrifos and another cholinesterase inhibitor found a relationship between chlorpyrifos exposure and impaired learning and memory.

Dominah GA, McMinimy RA, Kallon S, Kwakye GF. Acute exposure to chlorpyrifos caused NADPH oxidase mediated oxidative stress and neurotoxicity in a striatal cell model of Huntington's disease. *Neurotoxicology*. 2017;60:54-69. doi:10.1016/j.neuro.2017.03.004.

- Exposed a mouse model of Huntington disease to chlorpyrifos and found mutant HD cells were more susceptible to chlorpyrifos toxicity than wild type cells.

Faria M, Prats E, Padrós F, Soares AMVM, Raldúa D. Zebrafish is a predictive model for identifying compounds that protect against brain toxicity in severe acute organophosphorus intoxication. *Arch Toxicol*. 2017;91(4):1891-1901. doi:10.1007/s00204-016-1851-3.

- Demonstration that zebrafish are a good model for evaluating neurodevelopmental changes from chlorpyrifos as well as for evaluating potential treatments.

Peiris DC, Dhanushka T. Low doses of chlorpyrifos interfere with spermatogenesis of rats through reduction of sex hormones. *Env Sci Poll Res Int*. 2017;24(26):20859-20867. doi:10.1007/s11356-017-9617-x.

- Rat study showing decreased male fertility after chlorpyrifos exposure.

Qiu X, Nomichi S, Chen K, et al. Short-term and persistent impacts on behaviors related to locomotion, anxiety, and startle responses of Japanese medaka (Oryzias latipes) induced by acute, sublethal exposure to chlorpyrifos. *Aquat Toxicol*. 2017;192:148-154. doi:10.1016/j.aquatox.2017.09.012.

- Exposed fish to a large acute (sublethal) chlorpyrifos dose and noted some behavioral effects persisting up to three weeks after, with some relation to AChE activity.

Van den Brink PJ, Klein SL, Rico A. Interaction between stress induced by competition, predation, and an insecticide on the response of aquatic invertebrates. *Environmental Toxicology and Chemistry*. 2017;36(9):2485-2492. doi:10.1002/etc.3788.

- Fish study looking at the relationship between stress and chlorpyrifos toxicity found that predation stress actually decreased chlorpyrifos toxicity.

Zhang J, Liu L, Ren L, et al. The single and joint toxicity effects of chlorpyrifos and beta-cypermethrin in zebrafish (Danio rerio) early life stages. *J Hazard Mater*. 2017;334:121-131. doi:10.1016/j.jhazmat.2017.03.055.

- Exposure of zebrafish to chlorpyrifos and other pesticides. Chlorpyrifos exposure increased malformations and death of zebra fish larvae.

Part 1d. Bench Studies

Adigun AA, Ryde IT, Seidler FJ, Slotkin TA. Organophosphate exposure during a critical developmental stage reprograms adenylyl cyclase signaling in PC12 cells. *Brain Res*. 2010;1329:36-44. doi:10.1016/j.brainres.2010.03.025.

- In cells that were differentiating, chlorpyrifos exposure changed adenylyl cyclase signaling pathways.

Lee JE, Lim MS, Park JH, Park CH, Koh HC. Nuclear NF-κB contributes to chlorpyrifos-induced apoptosis through p53 signaling in human neural precursor cells. *Neurotoxicology*. 2014;42:58-70. doi:10.1016/j.neuro.2014.04.001.

- This study exposed human neural precursor cells to chlorpyrifos and found multiple chlorpyrifos-induced changes at the molecular level that are similar to changes from other neurotoxicants.

Moyano P, del Pino J, Anadon MJ, Díaz MJ, Gómez G, Frejo MT. Toxicogenomic profile of apoptotic and necrotic SN56 basal forebrain cholinergic neuronal loss after acute and long-term chlorpyrifos exposure. *Neurotoxicol Teratol*. 2017;59:68-73. doi:10.1016/j.ntt.2016.10.002.

- Bench study showing that chlorpyrifos causes apoptosis and necrosis partially through acetylcholinesterase overexpression, but also via other mechanisms including alterations of signaling pathways at low levels of chlorpyrifos exposure. Those alterations seem to be time and dose dependent.

Wu X, Yang X, Majumder A, et al. From the Cover: Astrocytes Are Protective Against Chlorpyrifos Developmental Neurotoxicity in Human Pluripotent Stem Cell-Derived Astrocyte-Neuron Cocultures. *Toxicol Sci*. 2017;157(2):410-420. doi:10.1093/toxsci/kfx056.

- Bench study that evaluated chlorpyrifos toxicity to neurons only and in a mixture of neurons and astrocytes. Astrocyte presence had a somewhat protective effect for neurons, likely through the cytochrome P450 enzymes.

Part Two: Important Organophosphate Studies to Consider

Part 2a. Relevant Review Articles

Banks CN, Lein PJ. A review of experimental evidence linking neurotoxic organophosphorus compounds and inflammation. *Neurotoxicology*. 2012;33(3):575-584. doi:10.1016/j.neuro.2012.02.002.

- 2012 review of inflammation and organophosphates, suggests inflammation as a potential mechanism for organophophate induced neurotoxicity

Bjørling-Poulsen M, Andersen HR, Grandjean P. Potential developmental neurotoxicity of pesticides used in Europe. *Environ Health*. 2008;7(1):50. doi:10.1186/1476-069X-7-50.

- Review of developmental neurotoxicity of a number of pesticides, including chlorpyrifos

Flaskos J. The neuronal cytoskeleton as a potential target in the developmental neurotoxicity of organophosphorothionate insecticides. *Basic Clin Pharmacol Toxicol*. 2014;115(2):201-208. doi:10.1111/bcpt.12204.

- Review of organophosphate metabolite effects on the neuronal cytoskeleton

González-Alzaga B, Lacasaña M, Aguilar-Garduño C, et al. A systematic review of neurodevelopmental effects of prenatal and postnatal organophosphate pesticide exposure. *Toxicol Lett*. 2014;230(2):104-121. doi:10.1016/j.toxlet.2013.11.019.

- 2014 review of neurodevelopmental effects of organophosphates

Hernández AF, González-Alzaga B, López-Flores I, Lacasaña M. Systematic reviews on neurodevelopmental and neurodegenerative disorders linked to pesticide exposure: Methodological features and impact on risk assessment. *Environment International*. 2016;92-93:657-679. doi:10.1016/j.envint.2016.01.020.

- Summary of 65 systematic reviews of pesticides and neurologic health effects.

Koureas M, Tsakalof A, Tsatsakis A, Hadjichristodoulou C. Systematic review of biomonitoring studies to determine the association between exposure to organophosphorus and pyrethroid insecticides and human health outcomes. *Toxicol Lett*. 2012;210(2):155-168. doi:10.1016/j.toxlet.2011.10.007.

- Systematic review of organophosphates and human health

Marsillach J, Costa LG, Furlong CE. Paraoxonase-1 and Early-Life Environmental Exposures. *Annals of Global Health*. 2016;82(1):100-110. doi:10.1016/j.aogh.2016.01.009.

- Review of PON1 activity and its relation to neurodevelopment and organophosphates, including that PON1 activity, which is important in chlorpyrifos metabolism, is markedly lower in neonates. Includes diagrams of the metabolism of chlorpyrifos in the body.

Muñoz-Quezada MT, Lucero BA, Barr DB, et al. Neurodevelopmental effects in children associated with exposure to organophosphate pesticides: a systematic review. *Neurotoxicology*. 2013;39:158-168. doi:10.1016/j.neuro.2013.09.003.

- Systematic review of neurodevelopmental effects of organophosphates.

Part 2b. Epidemiologic Studies

Cartier C, Warembourg C, Le Maner-Idrissi G, et al. Organophosphate Insecticide Metabolites in Prenatal and Childhood Urine Samples and Intelligence Scores at 6 Years of Age: Results from the Mother-Child PELAGIE Cohort (France). *Environ Health Perspect*. 2016;124(5):674-680. doi:10.1289/ehp.1409472.

- Study of a French longitudinal birth cohort looking at urinary organophosphate metabolites and intelligence at age 6. Found positive correlations with verbal comprehension and inverse correlations with working memory.

Coker E, Gunier R, Bradman A, et al. Association between Pesticide Profiles Used on Agricultural Fields near Maternal Residences during Pregnancy and IQ at Age 7 Years. *Int J Environ Res Public Health*. 2017;14(5):506. doi:10.3390/ijerph14050506.

- From the CHAMACOS cohort, looking at exposure to multiple pesticides during pregnancy (from publically available pesticide use data) and relationship to childhood IQ. Some of the neurodevelopmental decrements related to the pesticide exposure seem to be sub-additive.

Donauer S, Altaye M, Xu Y, et al. An Observational Study to Evaluate Associations Between Low-Level Gestational Exposure to Organophosphate Pesticides and Cognition During Early Childhood. *Am J Epidemiol*. 2016;184(5):410-418. doi:10.1093/aje/kwv447.

- Observational birth cohort in Cincinnati that did not find associations between organophosphate metabolites prenatally and measures of cognition in early childhood. Notably the cohort was high SES.

Eskenazi B, Kogut K, Huen K, et al. Organophosphate pesticide exposure, PON1, and neurodevelopment in school-age children from the CHAMACOS study. *Environmental Research*. 2014;134:149-157. doi:10.1016/j.envres.2014.07.001.

- Study from the CHAMACOS cohort relating organophosphate exposure (via urinary biomarkers), PON1 genotype and neurodevelopment, with neurobehavioral findings suggesting that children with pesticide exposures whose mothers were less able to metabolize the pesticides demonstrated higher degrees of neurotoxicity from in-utero exposure.

González-Alzaga B, Hernández AF, Rodríguez-Barranco M, et al. Pre- and postnatal exposures to pesticides and neurodevelopmental effects in children living in agricultural communities from South-Eastern Spain. *Environment International*. 2015;85:229-237. doi:10.1016/j.envint.2015.09.019.

- Cross sectional study in Spain that found inverse correlation between children's urinary DAP (organophosphate biomarker) levels and IQ results, as well as inverse correlation with modeled pesticide use during the postnatal period.

Gunier RB, Bradman A, Harley KG, Kogut K, Eskenazi B. Prenatal Residential Proximity to Agricultural Pesticide Use and IQ in 7-Year-Old Children. *Environ Health Perspect*. 2017;125(5):057002. doi:10.1289/EHP504.

- From the CHAMACOS cohort, assessed relationship between agricultural pesticide use near the mother's residence when the child was in utero (from pesticide use data) with IQ at age 7 and found decreases in IQ and verbal comprehension with increases in organophosphate use.

Ismail AA, Bonner MR, Hendy O, et al. Comparison of neurological health outcomes between two adolescent cohorts exposed to pesticides in Egypt. *PLoS ONE*. 2017;12(2):e0172696. doi:10.1371/journal.pone.0172696.

- Comparison of two similar cohorts of Egyptian adolescent pesticide applicators in 2005 and 2009, found that the earlier cohort had greater levels of butyryl cholinesterase depression.

Kongtip P, Techasaensiri B, Nankongnab N, et al. The Impact of Prenatal Organophosphate Pesticide Exposures on Thai Infant Neurodevelopment. *Int J Environ Res Public Health*. 2017;14(6):570. doi:10.3390/ijerph14060570.

- From the SAWASDEE cohort, they found a significant relationship between maternal prenatal organophosphate biomarkers and infant development.

Millenson ME, Braun JM, Calafat AM, et al. Urinary organophosphate insecticide metabolite concentrations during pregnancy and children's interpersonal, communication, repetitive, and stereotypic behaviors at 8 years of age: The home study. *Environmental Research*. 2017;157:9-16. doi:10.1016/j.envres.2017.05.008.

- From the Cincinnati birth cohort, looked at prenatal organophosphate exposure (using urinary biomarkers) and autism type behaviors. They found no relationship including no modification by PON1 genotype.

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- Case control study of children with autism and retrospectively reported prenatal folic acid intake and pesticide exposure and found that reduced folic acid intake when combined with pesticide exposure, increased the risk for autism in a supra-additive fashion.

Wang P, Tian Y, Wang X-J, et al. Organophosphate pesticide exposure and perinatal outcomes in Shanghai, China. *Environment International*. 2012;42:100-104. doi:10.1016/j.envint.2011.04.015.

- Study to assess pesticide exposures in China and relate prenatal exposure to birth outcomes. Found that increased urinary markers of organophosphates inversely associated with gestational length only in girls.

Wang Y, Zhang Y, Ji L, et al. Prenatal and postnatal exposure to organophosphate pesticides and childhood neurodevelopment in Shandong, China. *Environment International*. 2017;108:119-126. doi:10.1016/j.envint.2017.08.010.

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